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NEW SYNTHETIC ANTIMICROBIC PREPARATIONS

THE ANTIMICROBIC ACTIVITY OF SOME SALICYLANILIDE DERIVATIVES

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New Synthetic Antimicrobial Preparations.
The Antimicrobial Activity of Some Salicylanilide Derivatives.

by

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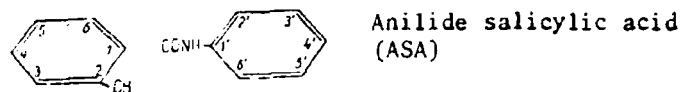
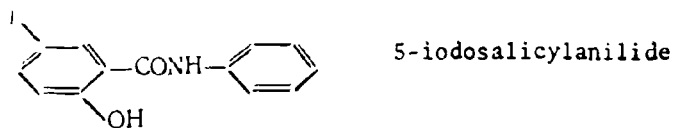
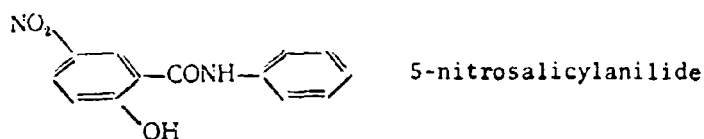
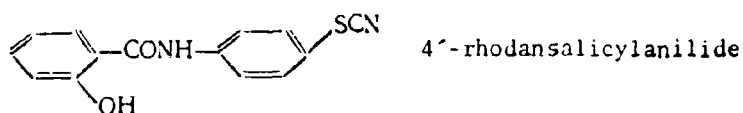
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NEW SYNTHETIC ANTIMICROBIC PREPARATIONS

THE ANTIMICROBIC ACTIVITY OF SOME SALICYLANILIDE DERIVATIVES

In the antibiotics laboratory of Kiev State University the antimicrobial and therapeutic properties of salicylanilide derivatives have been studied since 1956. During this time salicylanilide has been investigated as well as its chlorine and bromine derivatives, which possess good therapeutic properties; three preparations have already been approved by the Pharmacological Committee of the USSR Academy of Medical Sciences as new medical supplies and have been brought into production after clinical testing [1, 2]. In connection with this, there is no doubt in the conformity of a series of other cyanilide derivatives to the study. By this method we have also synthesized and studied the antimicrobial activity and toxicity of such derivatives as:



4'-rhodansalicylanilide is the original compound; as regards 5-nitrosalicylanilide and 5-iodosalicylanilide only data on its synthesis are encountered in the literature; the antimicrobial properties of these compounds have not been discussed [3].

A broad spectrum of test microbes were utilized for research on the microbial activity of these preparations, including bacteria, cocci, microbacteria *Candida albicans*, and also representatives of the pathogenic, phytopathogenic and saprophytic mycelial fungi. Research was carried out by the generally accepted method of serial dilution. The solvent was 0.1% alcohol.

4'-rhodansalicylanilide had the highest MBSC of all the salicylanilides that were tested in these experiments. ASA has already been recognized as an antifungus preparation from the class of salicylanilides, namely from its antimicrobial activity compared to other salicylanilides. The results of the experiments indicate that the minimal fungistatic concentration (MFSC) of 4'-rhodansalicylanilide is higher than the MFSC of ASA and for all fungi except *Aspergillus niger* (Table 1).

Table 1

Results of Research on the Antimicrobial Effect of Salicylanilide

Minimal bacteriostatic (MBSC) and minimal fungistatic (MFSC) concentrations in γ /ml

Microorganisms	4'-rhodan- salicylanilide	5-nitro- salicylanilide	5-iodosa- licylani- lide	Anilide of Sali- cylic acid (ASA)
<i>Staph. aureus</i> , wt. a) 209	0.1	200	10	100
<i>Staph. aureus</i> , wt. 5	3.3	100	3.3	100
<i>Staph. aureus</i> «Kee»	0.3	100	3.3	100
<i>Staph. albus</i>	0.3	100	3.3	100
<i>Staph. citreus</i>	0.3	100	3.3	100
<i>Micrococcus agilis</i>	3.3	1000	1000	100
<i>Sarcina flava</i>	3.3	100	3.3	—
<i>Bac. subtilis</i>	0.3	100	330	100
<i>Bac. mycoides</i>	0.3	100	33	1000
<i>Bact. pyocyanum</i>	330	0	0	0
<i>Bact. coli</i>	0	0	0	0
<i>Proteus vulgaris</i>	0	0	0	0
<i>Mycobact. B-5</i> a)	0.5	5	0.5	1000
<i>Mycobact. tuberculosis</i> , wt. hominis, Akademia 332	—	10	100	—
<i>Trich. gypsum</i>	0.6	5	10	10
<i>Epidermoph K-W</i>	0.1	2	10	10
<i>Microsporum lanosum</i>	3.3	2	100	100
<i>Candida albicans</i>	250	125	0	100
<i>Penicillium cyclop</i>	100	10	100	100
<i>Trichoderma lignor</i>	10	10	100	100
<i>Aspergillus niger</i>	330	33	100	100

Note. - Experiments were not performed.

a) strain

We utilized a broad spectrum of microorganisms (Table 2) for detailed study of 4'-rhodansalicylanilide. In all 28 tests, among which a majority of pathogenic fungi predominated, the preparation acted at significantly lower concentrations than salicylanilide (ASA).

Table 2
Antimicrobial Effect of 4-rhodansalicylanilide

Microorganisms	Minimal bacteria- static con- centration (MBSC) in γ/ml	Microorganisms	Minimal bacteria- static con- centration (MBSC) in γ/ml
<i>Bact. malvarum</i>	10	<i>Trichophyton crateriforme</i>	2.5
<i>Bact. Fridlandi</i>	10	<i>Trichophyton roseum</i>	10
<i>Bact. paratyphi A</i>	10	<i>Trichophyton equinum</i>	0.1
<i>Bact. prodigiosum</i>	0	<i>Trichophyton violaceum</i>	0.1
<i>Bac. mesentericus</i>	10	<i>Microsp. audouini</i>	0.1
<i>Bac. megaterium</i>	10	<i>Microsp. equinum</i>	0.1
<i>Staph. aureus C</i>	100	<i>Rh. nigricans</i>	10
<i>Micrococcus citreus</i>	0.1	<i>Penicillium cinerea</i>	10
<i>Vibrio Melanicos</i>	10	<i>Penicillium tardum</i>	10
<i>Pseud. fluorescens</i>	10	<i>Fusarium culmorum</i>	0.1
<i>Achorion quinqvearum</i>	0.1	<i>Fusarium avenaceum</i>	100
<i>Achorion Schönleini</i>	100	<i>Fusarium gibberilinum</i>	0.1
<i>Achorion gypseum</i>	0.1	<i>Fusarium gladioli</i>	10
<i>Trichophyton cylinum</i>	2.5	<i>Fusarium graminearum</i>	2.5

It should be noted that experiments investigating the antituberculosis effect of salicylanilides, which were carried out at the Institute of Tuberculosis and Chest Surgery of the World Health Organization of the USSR on pathogenic micobacteria (BK), showed that 5-nitrosalicylanilide displayed tuberculo-static activity in vitro at a concentration of 10 γ/ml. However, study of this preparation in a model of experimental tuberculosis in white mice did not reveal its chemotherapeutic activity.

Comparative study of the influence of serum on the activity of salicylanilide and its derivatives 4'-rhodan-, 5-iodo- and 5-nitrosalicylanilides showed that upon addition of 10% normal horse serum to MPB the antimicrobial effect of these substances decreased 10-100 times (Table 3). This is in agreement with literature data on the antimicrobial activity of salicylanilide derivative [4, 5].

Investigation of the toxicity of the salicylanilides which we studied showed that these compounds are not very toxic. Experiments were carried out in white mice by subcutaneous and peroral injections and in white rats by intraperitoneal injection. White mice tolerate 2 g per kg of live weight of 4'-rhodansalicylanilide and 5-iodosalicylanilide in castor oil by subcutaneous injection. Salicylanilide has significantly higher toxicity than its derivatives (Table 4).

Table 3
Effect of Normal Horse Serum on Bactericidal Effect of
Salicylanilides in Relation to Mycobacterium B-5

Compound	Minimal bacteriostatic concentration (MBSC) in γ /ml	
	MTB	MTB+10% normal horse serum
4'-rhodansalicylanilide	10	1000
5-nitrosalicylanilide	2.5	25
5-iodosalicylanilide	2.5	25
Anilide of salicylic acid (ASA)	100	1000

Table 4
Toxicity of Salicylanilides

Compound	Injection of MTD(in mg/kg)			LD-50	LD-100
	subcutaneous (in mice)	per os (in mice)	intraperitoneally (in rats)	per os	
4'-rhodansalicylanilide	2000	500	2000	3000	-
5-nitrosalicylanilide	700	700	800	1400	2000
5-iodosalicylanilide	2000	1000	1000	2500	3000
Salicylanilide (ASA)	500	500	500	750	

Note. -dose was not established for the poorly soluble 4'-rhodansalicylanilide.

Thus, 4'-rhodansalicylanilide, 5-nitrosalicylanilide and 5-iodosalicylanilide are slightly toxic substances with high antimicrobial effect. Therefore, research on salicylanilide and, in particular, 4'-rhodansalicylanilide merits detailed laboratory and clinical study. There is reason to expect that deeper study of these compounds, especially 4'-rhodansalicylanilide, will permit their utilization as new antimicrobial therapeutic preparations.

Conclusions

1. We have synthesized and studied the antimicrobial effect of salicylanilide derivatives: 4'-rhodansalicylanilide, 5-nitrosalicylanilide and 5-iodosalicylanilide.

2. All three of the salicylanilide derivatives studied are characterized by significant antimicrobial effect on gram positive bacteria, pathogenic and saprophytic fungi. They have no effect on gram negative bacteria. Their antimicrobial effect was studied in comparison to anilide salicylic acid (ASA).

3. 5-nitrosalicylanilide possesses fair antimicrobial activity, MBSC is like that of ASA (100 γ /ml); its fungistatic activity, MFSC (2.0-10 γ /ml) is higher than that of ASA (100 γ /ml).

4. 5-iodosalicylanilide has a MFSC equal to that of ASA (from 10 to 100 γ /ml), its antibacterial activity, MBSC (from 0.5 to 33 γ /ml) is higher than that of ASA (100 γ /ml).

5. 4'-rhodansalicylanilide possesses the highest antimicrobial effect of all the compounds studied; it is as good or better than antibiotics. The MBSC for gram positive bacteria and the MFSC for pathogenic hyphal dermatophytes, from 0.1 to 3.3 γ /ml. For *Candida albicans* (250 γ /ml) and saprophytic fungi (100-330 γ /ml) this preparation is not effective.

6. Microbial activity of these compounds decreases 10-100 times upon addition of 10% normal horse serum.

7. The salicylanilides which we studied possess low toxicity; the maximal tolerable dose (MTD) varies in the range 700-2000 mg/kg of live weight with various methods of injection.

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13. ABSTRACT

The authors have synthesized three new derivatives of salicylanilide: 5-nitrosalicylanilide, 5-iodosalicylanilide and 4-rhodansalicylanilide. The antimicrobic activity of 5-nitro- and 5-iodosalicylanilide (40-100 γ /ml) was found to be somewhat higher than that of salicylanilide. 4-rhodansalicylanilide has higher antimicrobic activity than salicylanilide: its MBSC and MFSC are 0.1-3.3 γ /ml. The salicylanilides investigated possess low toxicity. MTD varies from 700-2000 mg/kg of live weight for various methods of injection. The antimicrobic activity of the preparation is considerably lower upon addition of serum. Three other derivatives have already been approved by the pharmacological committee as new drugs.

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